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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,952	03/22/2002	Stephen H. Leppla	15280-4051US	4741

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,952	LEPPLA ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9, 11-14,18-22 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7, 9, 11-14, 18-22 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 2/14/2007 in response to the previous Non-Final Office Action (9/15/2006) is acknowledged and has been entered.

Claims 1, 7, 9, 11-14, 18-22 and 25-30 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of claims 1, 4, 8-9, 11-14, 18-22 and 25-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants arguments and the submission of the two journal references (Ke et al. J. Biol. Chem. 1977; 272: 20456-20462; and Ke et al. J. Biol. Chem. 272: 16603-16609).

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 8-9, 11-14, 18-22 and 25-30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (IDS, 1997) as evidenced by Klimpel et al. (PNAS 1992; 89: 10277-10281) in view of Bayley *et al.* (IDS, 1998).

Leppla *et al.* teach (column 115, lines 41-63) a method for targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: a) administering to the cell population a first compound comprising a first protein consisting essentially of: i) the translocation domain and the anthrax lethal factor (LF) binding domain of the native anthrax protective antigen (PA) protein, and ii) a ligand domain that specifically binds the first protein to a target on the surface of the cell population to bind the first

compound to said surface; and b) administering to the resultant cell population a second compound comprising a fusion protein or conjugate consisting essentially of: i) the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein, chemically attached to ii) a biological activity-inducing polypeptide to bind the second compound to the first compound on the surface of the cell population, internalize the second compound into the cell population, and effect the activity of the polypeptide therein. The patent further teaches (Column 116, lines 42-44, 53-56, and 63-64) that the ligand domain of the first compound can be either the ligand domain of the native anthrax protective antigen (PA) protein or growth factor, or an antibody, wherein the antibody is a single chain antibody. Furthermore, Leppla *et al.* disclose (column 115, lines 64-67 and column 116, lines 40-41) that the anthrax protective antigen (PA) binding domain of the second compound comprising at least the first 254 amino acid residues but less than all of the amino acid residues of the native anthrax lethal factor. Moreover, the patent teaches (column 116, lines 51-52) that the second compound may comprise the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein chemically attached to a polypeptide through a peptide bond. In addition, Leppla *et al.* teach (column 116, lines 49-52 and 57-62) that the polypeptide of the second compound is an enzyme or a toxin, wherein the toxin can be Pseudomonas exotoxin A (PE), A chain of Diptheria toxin, or shiga toxin. With regards to Pseudomonas exotoxin A, the patent teaches (column 17, lines 15+) that anthrax lethal toxin is linked to the ADP-Ribosylation Domain of Pseudomonas exotoxin. Leppla *et al.* also disclose (Abstract, last sentence) proteins including an anthrax protective antigen which has been mutated to replace the trypsin cleavage site with residues recognized specifically by the HIV-1 protease. Specifically, the patent teaches (column, 11, lines 10-13) PA proteins which have been mutated to replace R164 to 167 with an amino acid sequence recognized by the HIV-1 protease. In addition, the patent teaches (column 1, lines 24-26) that in a therapeutic or diagnostic setting, the used of an sFv may offer attractive advantages over the use of monoclonal antibodies. Lastly, Leppla *et al.* teach (column 15, lines 27-37) that this methodology can be used to specifically kill a tumor cell in a subject. Thus while Leppla et al. do not specifically teach that amino acid residues R164-167 is the furin recognized cleavage site of native protective antigen, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art because as evidenced by Klimpel et al. residues 164 to 167 of PA is a furin recognized cleavage site (abstract).

Leppla *et al.* does not disclose a mutated protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site. Nor do Leppla et al. teach that the cancer is a melanoma.

Bayley *et al.* teach (column 12, lines 13+) the construction of Ab-αHL conjugates and mutated two chain αHL conjugates, wherein a protease can be employed as an activator of inactive compounds, e.g. plasminogen activator, specifically urokinase-type plasminogen activator (uPA). Specifically, the patent teaches (column 12, lines 13+) that because cancer cells have been shown to secrete plasminogen activator, the protease cleavage site for plasminogen activator can be incorporated into the conjugate for specific activation of this cell type. In addition, the patent teaches that uPA is highly expressed in melanoma cells (column 13, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate a plasminogen activator-protease cleavage site in place of the native protective antigen furin-recognized cleavage site as a way of targeting a compound to a cancer cell over-expressing a plasminogen activator or plasminogen activator receptor. One would have been motivated to make this substitution because Bayley *et al.* teach that it is well known in the art that a plasminogen activator, such as uPA, can be employed as an activator of an inactive agent such as the protective antigen protein of Leppla *et al.*. One of ordinary skill in the art would have reasonable expectation of success that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell because as evidenced by Bayley et al., cancer cells have been shown to secrete plasminogen activator.

In response to this rejection, Applicants assert that Dr. Leppla's declaration submitted with the response to the office action dated August 23, 2005 establishes that one of ordinary skill in the art would not have a reasonable expectation of success of practicing the claimed invention if the cited references were combined. In particular, Applicants assert that the Examiner has provided no reasoning as to why his own opinion should be substituted for that of an expert in the field of the invention, and therefore, has not properly considered the rebuttal evidence presented in the expert declaration. Specifically, in contrast to the Examiners conclusionary statement, Applicants assert that Dr. Leppla's declaration provides a specific scientific explanation of why an ordinary skilled artisan would have no reasonable expectation of success when combining the references. To

reiterate, Applicants assert that Dr. Leppla emphasized the importance of compatibility of the three dimensional structure of both a protease and its substrate in effecting the binding of a protease to its cleavage site on the substrate and subsequent proteolytic cleavage. For example, Applicants assert that Dr. Leppla states that one of skill in the art would not have expected the non-natively situated uPA cleavage site on the mutant protective antigen to come into contact with uPA, citing as one rationale the fact that the uPA cleavage site in the mutant protective antigen might not be positioned at an appropriate distance from the cell membrane to contact the uPA on the surface of the target cell. Accordingly, Applicants assert that the skilled artisan would not have expected the uPA cleavage site to be accessible to uPA when the cleavage site is taken out of its normal three dimensional context within plasminogen and placed into a heterologous, non-naïve context such as in protective antigen. Applicants further assert that Dr. Leppla's declaration provides objective secondary evidence of non-obviousness and the Examiner has not properly considered the data presented in Dr. Leppla's declaration as evidence of nonobviousness based on unexpectedly advantageous properties. For example, Applicants assert that the data presented in Dr. Leppla's declaration unequivocally demonstrates that the claimed mutant protective antigens are surprisingly effective for the delivery of a compound to tumors overexpressing uPA in vivo.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that the Examiner has not properly considered the rebuttal evidence presented in the expert declaration submitted in response to the office action dated August 23-2005, the Examiner acknowledges, as stated in the previous office action (page 9), that the level of success is often difficult to predict in view of the three dimensional structure. However, the Examiner recognizes that while the declaration states that the uPA cleavage site in the mutant PA might not be positioned at the appropriate distance from the cell membrane to contact the uPA on the surface of the target cell, one to the three requirements for a 103 rejection is a **reasonable, not absolute**, expectation of success in view of the references cited. In the instant case, Leppla et al. disclose targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising administering a protective antigen which has been mutated to replace the "native" trypsin cleavage site, e.g., furin cleavage site, with residues recognized specifically by the HIV-1 protease, wherein this methodology can be applied to specifically killing a tumor cell in a subject, whereas Bayley et al. teach that the incorporation of a

uPA recognized cleavage site into an inactive compound is made active by a plasminogen activator expressed on the cell surface of tumor cells. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the protective antigen as taught by Leppla et al. to include a uPA cleavage site in place of the furin cleavage site in view of the teachings of Bayley et al., one would achieve a method of specifically targeting tumor cells which express uPA in a subject. With regards to Applicants assertions that the data presented in Dr. Leppla's declaration is evidence of nonobviousness based on unexpectedly advantageous properties, the Examiner acknowledges Applicants allegations that there were unexpected results. However, the Examiner has carefully reviewed the Leppla Declaration and cannot find any basis for Applicants assertions of "unexpected advantageous properties". For example, the declaration presents experiments which demonstrate that the mutant protective antigens of the presently claimed invention are particularly effective for delivering a compound to target cells in vivo which amounts to a general allegation that the claims define a patentable invention (Declaration, page 4). However, the Declaration does not appear to set forth whether the effective delivery of a compound to tumors overexpressing uPA in vivo is really unexpected and does not appear to point out how the language of the claims patentably distinguishes them from the references. As such, Applicants allegations with respect to unexpected results, e.g., properties, are considered moot.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

Therefore, NO claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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